Considerations for Age-based Recommendations for Pneumococcal Conjugate Vaccine for Adults

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Policy Question

Should PCV13 be administered routinely to all adults 65 years of age or older?

Rationale for Considering PCV13 Use among Persons ≥65 Years Old

- ACIP universal recommendations for PPSV23 target this group
- CAPITA results for this age group
- Economic analyses favor PCV13 at age ≥65
  - Cost-effective strategies
  - Health benefits for all outcomes

ACIP 2012: GRADE results (pre-CAPITA)

- Evidence type/quality low (type 3)
  - Limited studies on efficacy against IPD (1 RCT in HIV+ adults)
  - No data on efficacy against pneumonia

- Uncertainty about the magnitude of expected health benefits and cost-effectiveness
  - Efficacy against non-bacteremic pneumonia unknown
  - Indirect effects from PCV13 use in children expected to reduce net benefits
  - Cost-effectiveness results sensitive to assumptions about PCV13 efficacy against pneumonia and expected herd effects

2012 ACIP decision:

Defer recommendation until critical data available on

1) efficacy against pneumonia

2) PCV13 herd effects

Critical Outcomes: Invasive Pneumococcal Disease (IPD) and Pneumococcal Non-bacteremic Pneumonia

Study/population	Endpoint	Vaccine Efficacy (95% CI)
CAPITA Adults 65+ Netherlands	PCV13-serotype IPD	75% (41%, 91%)
	PCV13-serotype non-bacteremic pneumonia	45% (14%, 65%)

What effect might we expect among persons ≥65 years old in the US?

CAPITA, ACIP June 2014

How many persons ≥65 years old would need to be vaccinated to prevent a single case of PCV13-type IPD or a single case of PCV13-type CAP?

Outcome (PCV13-type)	Baseline incidence (per 100,000 population)	Vaccine efficacy (95% CI)	Number needed to vaccinate[5]	
IPD	6.5[1]	75% (41%, 91%)[4]	20,400 (16,950 - 37,000)	Caveat: VE vs. placebo
Inpatient CAP	137.5[2]	45% (14%, 65%)[4]	1,620 (1,110 - 5,130)	Baseline estimates assume 10% of all CAP due to PCV13 - types
Outpatient CAP	201[3]	45% (14%, 65%)[4]	1,110 (760-3,500)	
Total CAP	-	-	656 (454-2,110)	

1. PCV13-type IPD rate among adults ≥65 years old in the US. CDC, ABCs, 2013
2. Simonsen et al Lancet Resp. Med 2014
3. Nelson et al. Vaccine 2008
4. CAPITA
5. Number-needed-to vaccinate (NNV) =1 / ($Rate_{baseline}$ – $Rate_{vaccinated}$)

Quality of Evidence for using PCV13 to prevent IPD and pneumonia (updated GRADE-2014)

Outcome	Risk of bias	Inconsis-tency	Indirectness	Impreci-sion	Quality of evidence
IPD	No serious	N/A	Serious	No serious	2[1]
Pneumonia	No serious	N/A	No serious	No serious	1

[1]Indirectness due to different comparison group

a. Placebo instead of PPSV
b. PPSV efficacy against IPD among older adults = 50-80%

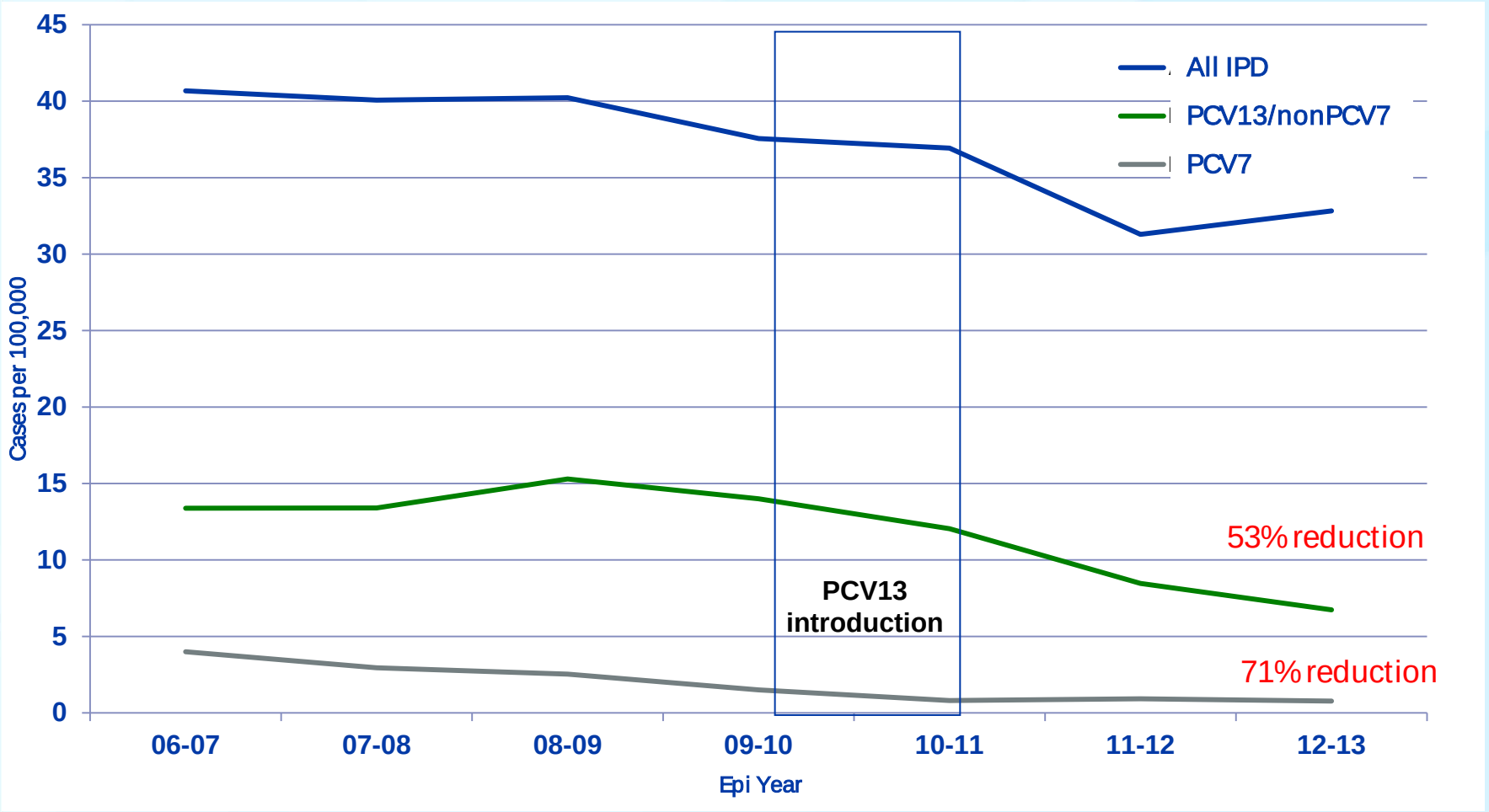
Quality of evidence (updated GRADE-2014)

Comparison	Outcome	Study Design (# studies)	Findings	Quality of evidence	Overall evidence type
PCV13 vs. no vaccination	IPD	RCT (1)	Decreased risk among vaccinated	2	
PCV13 vs. no vaccination	Pneumonia	RCT (1)	Decreased risk among vaccinated	1	2
PCV7 or PCV13 vs. PPSV23	Immunogenicity	RCT (6)	Response improved for PCV vs. PPSV23 or no difference	2	
PCV13 vs. PPSV23	Serious and systemic adverse events	RCT (3)	No difference or decreased risk with PCV13	1	

GRADE Conclusions in 2014 vs. 2012

	2012	2014	Comments
Is the evidence type/quality of evidence considered to be lower?	Y	N	- Data on efficacy against critical outcomes available
Is there uncertainty about the balance of benefits versus harms and burdens?	Y	N Y	**Short-term:** No uncertainty about the balance **Long-term:** Indirect effects likely reduce net benefits
Is there high variability or uncertainty in relative importance assigned to outcomes?	N	N	- General consensus reached on which outcomes are critical to prevent
Is there uncertainty about whether the net benefits are worth the costs?	Y	N Y	**Short-term:** No uncertainty **Long-term:** uncertainty about whether the net benefits are worth the costs due to continued herd effects

Herd effects on IPD: Incidence of Invasive Pneumococcal Disease Among Adults ≥65 Years by Serotype, 1998-2013



Active Bacterial Core Surveillance, unpublished

PCV13 herd effects on non-bacteremic pneumonia, 2011-2012

	All-cause pneumonia	Invasive pneumococcal disease	Non-invasive pneumococcal or lobar pneumonia	Empyema
<2 years	21% (14 to 28)*	64% (47 to 75)*	40% (14 to 59)*	50% (22 to 68)*
2–4 years	17% (7 to 27)*	55% (16 to 75)*	33% (–3 to 56)	46% (21 to 64)*
5–17 years	–3% (–20 to 11)	25% (–24 to 54)	51% (29 to 66)*	37% (13 to 54)*
18–39 years	12% (6 to 17)*	37% (20 to 51)*	32% (17 to 44)*	–8% (–25 to 6)
40–64 years	2% (–2 to 6)	13% (–1 to 26)	25% (16 to 33)*	–4% (–13 to 3)
≥65 years	3% (–1 to 6)	29% (16 to 40)*	34% (27 to 41)*	–1% (–10 to 7)

Data are percentage change (95% CI) according to our model. Assumes vaccine coverage at March, 2012 level.
*Significant reduction (p<0·05).

Table 3: Proportion of seasonal admissions to hospital averted by vaccination per season at coverage achieved in March, 2012

Simonsen et al Lancet Resp Med 2014

Indirect Effects

- PCV7 introduction led to near elimination of PCV7-type IPD among adults of all age groups
- Evidence of continued declines in PCV7-type IPD in adults due to herd effects
- Indirect effects of pediatric PCV13 program have further reduced the proportion of adult IPD and pneumonia caused by PCV13 types
- Studies report reduction in non-bacteremic pneumonia in adults following PCV7 and PCV13 introduction in children

Key point: The expected benefits of PCV13 use among adults will decline over time

Estimating PCV13 –type disease burden among adults 65 years or older in a setting of herd effects

	Estimated US cases without direct PCV13 use in adults		
Outcome (PCV13 type)	2013	2015 (20% reduction due to herd effects*)	2019 (86% reduction due to herd effects*)
IPD	2,660	2,130	370
Inpatient CAP	56,380	45,100	7,890
Outpatient CAP	82,410	65,930	11,540
Total CAP	138,790	111,030	19,430

*Based on post-PCV7 experience

Estimating cases potentially preventable among adults 65 years or older

	Estimated US cases potentially preventable	
Outcome (PCV13 type)	**2015** • **20%** reduction due to herd effects* • PCV13 direct effects** • Coverage **10% (5%-30%)**	**2019** • **86%** reduction due to herd effects* • PCV13 direct effects** • Coverage **30% (20%-60%)**
IPD	160 (80-480)	80 (50-170)
Inpatient CAP	2,030 (1,020-6,090)	1,070 (700 -2,130)
Outpatient CAP	2,970 (1,480-8,900)	1,560 (1,040 – 3,120)
Total CAP	5,000 (2,500-14,990)	2,630 (1,740 – 5,250)

*Based on post-PCV7 experience

**Assume PCV13 VE = 75% (IPD) and 45% (CAP)

PCV13 age-based recommendations: Summary of presented evidence

- Strong quality (type 2) of evidence supports the use of PCV13 among adults
  - PCV13 is safe for use among adults
  - PCV13 is efficacious in preventing IPD and non-bacteremic pneumonia among adults ≥65 years old
- Vaccine preventable disease burden remaining among adults 65 years or older
- Adding a dose of PCV13 to existing recommendations for PPSV23 is a cost-effective strategy and prevents illness among adults ≥65 years old
- Herd effects will continue to reduce PCV13-type disease burden and limit the utility of PCV13 use among adults in the long term

Policy options under consideration

- Add a dose of PCV13 at age ≥ 65 years to currently recommended PPSV23 regimen
  - PCV13 dose followed by a dose of PPSV23 at age ≥ 65 years
  - Risk-based recommendations for PCV13 and PPSV23 use remain unchanged

- Replace a dose of PPSV23 at age ≥ 65 years with a dose of PCV13
  - PCV13 at age ≥ 65 years
  - Risk-based recommendations for PCV13 and PPSV23 use remain unchanged

Desirable characteristics of pneumococcal vaccine for universal use among adults ≥65 years

	PCV13	
• Prevents IPD	+	• 75% reduction in vaccine type IPD
• Prevents non-bacteremic pneumonia	+	• 45% reduction in vaccine type non-bacteremic pneumonia
• Provides adequate coverage of serotypes causing disease	+/ --	• Yes, in the short-term • Unclear, long-term (herd effects)
• Allows for policy change that is simple to implement	--	• Policy options under consideration add complexity to current PCV/PPSV recommendations • Simplified strategies result in more IPD
• Cost-effective	+/ --	• Yes, short-term • Not cost-effective in a setting of fully observed herd effects

PCV13 age-based recommendations: Work Group Conclusions

- In the short-term, a recommendation for universal PCV13 use is warranted
- In the long-term, continued herd effects may limit the utility of a universal recommendation
- Policy options under consideration add complexity to current PCV13/PPSV23 recommendations
  - appropriate sequence and intervals between PCV13 and PPSV23
  - previous PCV13 and/or PPSV23 history
- Need to draft policy language addressing the concerns around
  - the complexity of current pneumococcal recommendation
  - time limited utility of universal PCV13 use
- Opportunity to prevent disease during the 2014-2015 respiratory season; timely implementation may require a decision before October ACIP meeting

Questions to ACIP

- What concerns do you have about the proposed policy options?
- How should the expected decline in the utility of the recommendation influence PCV13 recommendations?
- How feasible would it be to have a time limited recommendation?

Policy options under consideration

- Add a dose of PCV13 at age ≥ 65 years to currently recommended PPSV23 regimen
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